Pacing the right ventricle: To pace or not to pace?

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A number of important clinical trials have recently reported on clinical outcomes associated with different cardiac pacing modalities.1–5 As a consequence of these publications, concerns about the possible deleterious effects of right ventricular (RV) apical pacing, even in an atrioventricular (AV) synchronous mode, have arisen.6,7 There have even been calls to consider left ventricular (LV) or biventricular (BiV) pacing as the optimal lead configuration for pacing systems in patients without congestive heart failure (CHF). We recently participated in a debate on this topic and felt that it was important to objectively assess the evidence for and against employing RV apical pacing as the standard for ventricular pacing lead location.

The case against RV pacing

Incidence of LV dysfunction with RV pacing

Unfortunately, the true incidence of deterioration of ventricular function after initiation of RV pacing in patients with baseline normal LV function remains difficult to estimate. Large prospective studies have not been conducted to assess changes in ventricular function over time after pacemaker implantation. In a study of 24 young patients (mean age 19.5 years) receiving RV apical pacing, echocardiograms were obtained at follow-up (at 1–19 years) and compared with 33 normal subjects (mean age 16.4 years).8 LV fractional area of change was lower among paced patients ($P = .002$). However, in this population it is difficult to totally ascribe the reduction in LV function to RV pacing rather than to the progression of the underlying heart disease. In a retrospective review of 44 patients with moderate-severe heart failure (LV ejection fraction $[$LVEF$] 30\% \pm 13\%$), 44% of patients who were paced in the ventricle after implantation of a dual-chamber implantable cardioverter-defibrillator (ICD) developed worsening heart failure compared with only 5% of patients who were not paced ($P = .01$).9 Three (12%) of the RV paced group required hospitalization for treatment of heart failure, which was reversed after reprogramming to the VVI mode. Deterioration of LVEF has recently been reported in association with RV pacing compared with BiV pacing after AV junction ablation for atrial fibrillation. The LVEF fell (44.9% at baseline to 40.7% at 6 months) during RV pacing in 67 patients, whereas the LVEF remained unchanged over time during BiV pacing in 76 patients ($P = .03$).10 However, the vast majority of these patients had LV dysfunction at baseline. Information on changes in LVEF in patients with normal LV function has not yet been reported.

Randomized trials comparing ventricular- and atrial-based (“physiologic”) pacing

A number of prospective randomized trials have compared ventricular pacing to atrial or dual-chamber pacing on cardiovascular outcomes. The clinical characteristics of several of these study populations are summarized in Table 1. Andersen et al randomized 225 patients with sick sinus syndrome to AAI or VVI pacing.11 Over an 8-year follow-up, atrial pacing was associated with higher overall survival ($P = .045$) and survival from cardiovascular death ($P = .0065$) compared with ventricular pacing. In addition, atrial pacing was associated with less atrial fibrillation (AF) ($P = .012$), chronic AF ($P = .004$), thromboembolism ($P = .023$), and symptomatic heart failure.

The Canadian Trial of Physiologic Pacing Investigators randomized 2568 patients to ventricular (VVI[R]) or physiologic pacing (DDD[R] or AAI[R]).12 Over 3-year follow-up, there was no improvement in the primary endpoint of stroke or cardiovascular death with dual-chamber pacing. Physiologic pacing was associated with a reduction in paroxysmal and persistent AF, and this effect persisted over 6 years of follow-up.13 Hospitalization for heart failure was similar in the physiologic and ventricular pacing groups. No significant differences in AF or CHF were observed be-
The majority of patients were male, mean age 68 years, with severely depressed LV function and a marked intraventricular conduction delay (Table 1). These patients did not have symptomatic bradycardia as an indication for intervention suggesting that we should now investigate cardiac resynchronization therapy for primary prevention of adverse cardiovascular outcomes in patients who need to be paced in the ventricle most of the time.3

The Dual-Chamber and VVI Implantable Defibrillator (DAVID) Trial Investigators randomized 506 patients who had received a dual-chamber ICD to ventricular backup pacing at 40 bpm or to dual-chamber rate-responsive pacing at 70 bpm.1 The majority of patients were male, mean age 65, with a history of coronary artery disease, prior myocardial infarction, and significant LV dysfunction. Half of the patients had New York Heart Association (NYHA) functional class I symptoms, and only 12% had NYHA class III or IV symptoms. The mean QRS duration was 120 ms, but 30% had a QRS duration >130 ms. The primary outcome measure, death or hospitalization for new or worsened heart failure, was lower in the VVI-40 group (relative hazard 1.61, range 1.06–2.44, P = .03). At 1 year, the rate of hospitalization for CHF was 13.3% in the VVI-40 group, compared with 22.6% in the DDDR-70 group. Patients more frequently paced were more likely to experience an adverse outcome. These investigators concluded that conventional RV pacing in the DDD mode was contraindicated in this patient population without a bradycardia pacing indication. This study was accompanied by an editorial arguing for simplicity in pacing approaches in this population by minimizing ventricular pacing rather than considering a more expensive and complicated approach of BiV pacing.6

Nielsen et al randomized 177 patients with sick sinus syndrome to AAIR pacing or DDDR pacing with a short (≤150 ms) or long (300 ms) AV interval.5 This study was stopped prematurely, not because of achieving a prespecified endpoint, but because of the initiation of a multicenter trial comparing AAIR with DDDR pacing in Denmark. The investigators reported that DDDR pacing was associated with left atrial dilatation, a significant reduction in LV fractional shortening over time, and a higher incidence of AF compared with AAIR pacing.5,16 The investigators concluded that dual-chamber pacing even with a long AV delay caused ventricular dysfunction in this patient population and argued for more widespread use of AAIR pacing in this patient population. This study was accompanied by an editorial suggesting that we should now investigate cardiac resynchronization therapy for primary prevention of adverse cardiovascular outcomes in patients who need to be paced in the ventricle most of the time.7

The COMPANION Investigators reported a reduction in death or hospitalization for heart failure in patients randomized to receive a BiV pacemaker or ICD compared with patients randomized to best medical therapy for heart failure.3 The majority of patients were male, mean age 68 years, with severely depressed LV function and a marked intraventricular conduction delay (Table 1). These patients did not have symptomatic bradycardia as an indication for cardiac pacing. The clinical characteristics of this study population are similar to other patient populations receiving BiV pacing therapy for the management of symptomatic

### Table 1 Clinical characteristics of study populations

<table>
<thead>
<tr>
<th>Compan</th>
<th>DAVID</th>
<th>CTOPP/MOST</th>
<th>AAI vs. DDD Danish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td>New York Heart Association III (%)</td>
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<tr>
<td>QRS duration (ms)</td>
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<td>118</td>
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</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
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<td>27</td>
<td>Normal</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
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<td>69</td>
<td>25</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia/ventricular fibrillation (%)</td>
<td>None</td>
<td>100</td>
<td>&lt;1</td>
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NR = not reported.
heart failure. These investigators concluded that reduction in the combined endpoints of death and heart failure hospitalizations was primarily due to cardiac resynchronization therapy (CRT), since CRT and CRT with an ICD resulted in similar effects.

Why might RV pacing be detrimental?

Potential causes of the detrimental effect of RV apical pacing on LV function include pacing-induced LV dysynchrony secondary to the abnormal activation sequence, pacing-induced mitral regurgitation and/or pacing-induced abnormalities of myocardial blood flow.17–20 RV apical pacing has been reported to alter LV papillary muscle function, changing the timing sequence of the mitral valve apparatus, thus causing mitral regurgitation.18 BiV pacing has been reported to improve severe mitral regurgitation induced by RV pacing.19 Nielsen et al also reported that regional myocardial blood flow and LVEF were lower in 30 patients with sinus sinus syndrome randomized to AAI or DDD pacing compared with VVI pacing.20

The case for continued use of RV leads

Limitations of recent clinical trials

The MOST Study Investigators’ observations raise genuine concern about RV apical pacing precipitating ventricular dysfunction and/or AF in the population of patients with sinus node dysfunction as the primary indication for pacing.4 This study, however, has significant limitations. Many patients would have been candidates for AAIR pacing, thus preventing the need for RV pacing. Most patients with sinus node dysfunction have intrinsic AV conduction and few have concomitant intraventricular conduction delays (Table 1). It has been estimated that up to 20% of patients with sinus node disease as the primary indication for pacing are candidates for AAIR pacing. Even those patients with AV node conduction abnormalities have intrinsic AV conduction most of the time. The pacemakers employed in this study had a number of technical limitations. To program on mode switching or rate response with higher upper tracking rates, one was forced to program very short rate-adaptive AV delays and relatively short-paced and sensed AV intervals, thus imposing a high burden of ventricular pacing in this population that was unnecessary. From review of ECGs in 100 consecutive patients just before pacemaker implantation at our institution, 76% were in sinus rhythm with intrinsic AV conduction, whereas 20% had high-grade AV block and 4% were in AF. Twenty percent had an intraventricular conduction delay (AM Gillis, unpublished data). On the basis of all the data available from clinical trials in the pacemaker population, it is clear that most patients do not need to be paced in the ventricle all the time and it is quite likely that many do not require ventricular pacing most of the time. Given that the deleterious effects of ventricular pacing on the incidence of AF and CHF are only observed when the ventricles are paced >40%–50% of the time, approaches aimed at minimizing RV pacing should be successful in preventing adverse cardiovascular outcomes in many pacemaker patients.

The DAVID Study evaluated patients with ICDs but without symptomatic bradycardia as an indication for pacing.1 This study included patients with significant LV dysfunction but intact AV conduction. Some had intraventricular conduction delays but not to the magnitude reported in the cardiac resynchronization therapy trials for patients with CHF. Patients randomized to the DDDR mode were more likely to be paced in the ventricle as no systematic effort was made to prolong the programmed AV delay in an effort to minimize ventricular pacing and the usual AV delayed programmed was 180 ms. Whether faster heart rates in the DDDR group secondary to a higher lower programmed rate (70 bpm) and rate-response programming contributed to the higher incidence of heart failure remains uncertain. These patients did not need to be paced in the ventricle, and the only inescapable conclusion from this study is that we should avoid ventricular pacing in patients with intrinsic AV conduction in the setting of LV dysfunction. It is quite possible that LV pacing or BiV pacing in this study population would have resulted in prolonged ventricular conduction times compared with native conduction that could also lead to ventricular dyssynchrony and to worsening ventricular function.

The Nielsen et al study has some significant limitations.5 It was stopped early, and less than 40% of the original number of patients estimated to be needed to show a difference in LV function were enrolled. The major outcome of the paper is based on changes in LV fractional shortening measured by M mode echocardiography between the groups. Fractional shortening is an inappropriate surrogate of LV ejection fraction in paced patients. By definition, RV apical pacing creates paradoxical septal motion. An increase in LV end systolic dimension would thus be expected but this does not necessarily imply that the LV systolic function is depressed. Indeed, no differences in the incidence of heart failure were noted among the three groups. Furthermore, the fractional shortening measured at the end of the study was similar in all groups. Fractional shortening decreased over time in all groups, although the decrease was only statistically significant in the DDDR group with a short AV delay, reflecting a slightly lower variance of fractional shortening in this group. However, it seems inappropriate to conclude that ventricular pacing caused LV dysfunction based on changes in fractional shortening from 0.39 ± 0.08 to 0.36 ± 0.09 in the DDDR group with a short AV delay compared with changes in fractional shortening from 0.39 ± 0.07 to 0.36 ± 0.10 in the AAIR group. Indeed, these investigators report that LVEF measured by two-dimensional echocardiography decreased significantly over time in both the AAIR
and DDDR groups. Yet the investigators dismiss these observations, suggesting that this measure has not been validated in clinical studies. In contrast, we would conclude that fractional shortening is not an acceptable surrogate of LV systolic function comparing one group paced in the RV with another unpaced in the RV. The data do not support the conclusion that DDDR pacing contributes to LV dysfunction in this study population. The observations in this study support the fact that ventricular pacing even in an AV synchronous mode predisposes to AF. However, these observations cannot be directly extrapolated to the conclusion that RV apical pacing compared with other ventricular pacing sites causes AF. Pacing at other ventricular sites in this population with intrinsic AV conduction and normal His Purkinje conduction may well produce similar results by virtue of causing ventricular dyssynchrony secondary to imposed delayed and abnormal ventricular contractile patterns.21

**Might LV/BiV pacing be harmful in some patients?**

Even in the best of centers, LV lead placement via the coronary sinus is only 90%–94% successful.22 The risk of a significant complication, including lead dislodgement, coronary sinus dissection, or perforation, is approximately 10%.22 LV pacing thresholds are substantially higher than RV pacing thresholds. Thus, LV or BiV pacing will consume more energy and reduce longevity of implanted devices. The resources required for LV pacing compared with RV pacing are greater in terms of cost, time of implant, follow-up, and need for replacement over time. There is concern that LV epicardial pacing via the coronary sinus may precipitate ventricular proarrhythmia in some patients.23,24 LV or BiV pacing may also have detrimental hemodynamic effects in some patients compared with RV pacing.21 Approximately 20%–30% of patients with heart failure do not benefit from cardiac resynchronization therapy.22 Identification of patients most likely to benefit from this more complicated therapy would be ideal before contemplating such an approach in the elderly patient without heart failure.

**Implementing clinical trial results into clinical practice**

The DAVID, MOST, and Danish studies support the concept of minimizing ventricular pacing whenever possible. The AAIR mode should be considered for patients with sinus node dysfunction, a normal PR interval, and an intraventricular conduction delay <120 ms.25 In patients with sinus node dysfunction and intrinsic AV conduction, the risk of progression to heart block is 0.6% per year (range 0%–4.5%).25 Current pacemakers have algorithms to promote intrinsic AV conduction, which have been demonstrated to substantially reduce the proportion of pacing in the ventricle. Algorithms that promote mode switching from DDDR to AAIR are being introduced into new pacemaker technology. Whether these new algorithms will provide incremental benefit for minimizing ventricular pacing compared with the existing AV interval search hysteresis algorithms remains to be determined.

**What about patients who do or might need ventricular pacing?**

In DDDR devices, programming long AV delays may limit upper-rate programming with a decrease in 2:1 block rate. To compensate, post ventricular atrial refractory period (PVARP) may need to be reduced, which may increase susceptibility to pacemaker-mediated tachycardias. In some devices, DDIR programming may allow longer AV delays. However, in patients with AV block and sinus rate above the lower rate limit, the pacemaker would function essentially as a VVIR pacemaker and competitive atrial pacing may occur during sensor-driven pacing. Many current devices incorporate search AV hysteresis algorithms that may facilitate intrinsic conduction in DDDR mode. However, despite novel algorithms to allow longer AV delays or DDIR pacing, ventricular pacing may still occur in patients with long intrinsic PR intervals.

**Alternate RV pacing sites**

Alternate RV pacing sites, including the RV septum and RV outflow tract, have been compared with apical RV pacing. Some studies suggest that these locations are associated with preserved cardiac hemodynamics compared with apical RV pacing.26–28 However, some studies suggest no benefit of these alternate RV sites.29,30 Some studies suggest that pacing at the RV site associated with the shortest intraventricular conduction delay is associated with the best hemodynamic effect.26,31 Abnormalities of myocardial perfusion also have been observed in some patients treated with long-term RV apical pacing compared with RV outflow tract pacing.26,31 Investigators have also reported that depression of LVEF associated with RV apical pacing may not be observed until late after treatment with RV apical pacing. Hemodynamic impairment from RV apical pacing may not become fully manifest until after some months or even years. This may explain why some randomized clinical studies comparing RV apical pacing with RV outflow tract pacing have failed to show a significant benefit, particularly if follow-up was short.30,32 Patients with intact AV conduction and normal His Purkinje conduction may be more likely to experience preserved cardiac hemodynamics with RV septal pacing compared with RV apical pacing.27 However, this concept needs to be tested in a larger patient population. In selected patients with intact infraHisian conduction, His-bundle pacing, if achievable, may be an attrac-
tive option. However, currently, placement of pacing leads at the His bundle remains difficult with current tools.

**Alternate LV pacing sites**

The median age of the pacemaker population is 73 years, and >35% of patients requiring pacemakers are >80 years of age at initial implant. The majority of these patients have normal LV function and preserved AV and His Purkinje conduction. Would LV pacing or BiV pacing be superior to RV pacing in this population? At present there are limited data comparing RV pacing to LV or BiV pacing in the absence of significant LV dysfunction. Some data from small studies suggest a potential benefit. However, this needs to be confirmed in larger prospective trials. At present, there are no data to support the concept of either LV or BiV pacing for prevention of CHF or AF in patients with a normal ventricular function and intact AV conduction.

What are the lessons learned from clinical trials? The DAVID study teaches us that we should not pace the ventricles unless required. The MOST and DAVID studies teach us that we should optimally program dual-chamber devices to promote intrinsic AV conduction and minimize ventricular pacing whenever possible. The Danish study reminds us to consider AAIR pacing where clinically indicated. If we adhere to these principals, we can effectively manage the majority of patients who require pacing for symptomatic bradycardia without embarking on a more costly and more complicated approach that requires implantation of a LV pacing lead. Whether alternate RV pacing sites or LV or BiV pacing is the optimal strategy for managing patients with intraventricular conduction delays in the absence of significant ventricular dysfunction requires further study.

**References**